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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Drug Use Review

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Subject: Beyaz Drug Utilization Review

Drug Name(s):   Beyaz (drospirenone/ethinyl estradiol/levomefolate
                                        calcium tablets**)**

Application Type/Number: NDA 22-532

Applicant/sponsor: Bayer HealthCare Pharmaceuticals Inc.

OSE RCM #:   2012-834

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CONTENTS

EXECUTIVE SUMMARY

This review examines drug utilization for Beyaz (drospirenone/ethinyl estradiol/ levomefolate calcium tablets) and other drospirenone-containing contraceptive products in the pediatric population stratified by age (0-13,   14-17 years) and adults 18 years or older from September 1, 2010 through March 31, 2012.

- Approximately 18.9 million prescriptions for drospirenone-containing contraceptive products were dispensed and approximately 2.7 million patients received a dispensed prescription in the outpatient retail pharmacy setting.

- Beyaz was the fifth most frequently dispensed medication out of the selected market, accounting for approximately 8% of drospirenone-containing contraceptive products during the review period.

- Approximately 1.6 million prescriptions and 326,000 patients received a dispensed prescription for Beyaz from September 2010 through March 2012.

- Beyaz prescriptions dispensed to the pediatric population (age 0-17 years) accounted for 169,000 prescriptions and 39,000 patients (11% of total prescriptions and 12% of patients) for the entire review period.

- Obstetrics/Gynecology (Ob/Gyn) was the top prescribing specialty for Beyaz, Pediatricians accounted for <1% of the Beyaz prescriptions dispensed.

- "Dysmenorrhea" (ICD-9 625.3) followed by "Contracep Mgmt-Counsel" (V250.0) were the most common diagnosis codes for pediatric patients aged 14-17 years at 43% and 22% of Beyaz drug use mentions, respectively.

- Among pediatric patients 0-13 years of age, "Premenopause Menorrhagia" (ICD-9 627.0) was the only common diagnosis code associated with the use of Beyaz during the review period, however the number of mentions was below the acceptable count allowable to provide a reliable estimate of national use and should therefore be interpreted with caution.

1   INTRODUCTION

The Office of Pediatric Therapeutics (OPT), and Pediatric and Maternal Health Staff (PMHS) have requested a review of drug utilization patterns for Beyaz in preparation for mandatory safety reporting under the Pediatric Research Equity Act (PREA) at the September 2012 Pediatric Advisory Committee Meeting. The drug utilization data are requested to provide background and context for discussions at the advisory committee meetings. Using the currently available proprietary drug utilization databases, this review describes outpatient retail pharmacy utilization for Beyaz and other drospirenone-containing contraceptive products, from September 1, 2010 through March 31, 2012.

1.1 BACKGROUND

Beyaz (drospirenone/ethinyl estradiol/levomefolate calcium tablets**)** is an oral combined hormonal contraceptive containing folate approved for marketing on September 24, 2010 under NDA 22-532. FDA-approved indications include[1]:

• Prevent pregnancy

• Treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception.

• Treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control.

• Raise folate levels in women who choose to use an oral contraceptive for contraception.

DEPI II provided a review of national patterns of drug utilization for Yasmin, Yaz and other drospirenone-containing contraceptive products in November 2011. Findings from the review show the estimated number of prescriptions dispensed for drospirenone-containing contraceptive products decreased, as a whole, from a peak in use of nearly 18.4 million prescriptions in year 2008 (21% of the combined hormonal contraceptive market) to 12.9 million prescriptions in year 2010 (16% of the combined hormonal contraceptive market). [2]

1.2 PRODUCT LABELING

In April 2012, the labeling for Beyaz as well as Yasmin, Yaz, and Safyral was updated with a new safety warning that combined oral contraceptives containing drospirenone may be associated with a higher risk of venous thromboembolism than other contraceptives containing levonorgestrel or some other progestins.

Table 1: Indications of Drospirenone-Containing Products[3]

Trade Name	Application Number	Original Approval Date	Dosage Form and Dose	Indications
Drospirenone 3 mg, ethinyl estradiol 0.02 mg and levomefolate calcium 0.451 mg				
Beyaz®	NDA 22-532	9/24/2010	Oral tablet Dose: one tablet daily by mouth at the same time every day	-see Background Section 1.1
Drospirenone 3 mg, ethinyl estradiol 0.03 mg, and levomefolate calcium 0.451 mg				

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[1] Beyaz label http://www.beyaz.com/

[2] Greene, Patty. "Yasmin/Yaz (drospirenone-containing products) drug utilization" November 2011.

[3]Drospirenone Product labels. http://dailymed.nlm.nih.gov/dailymed/about.cfm

Trade Name	Application Number	Original Approval Date	Dosage Form and Dose	Indications
Safyral®	NDA 22-574	12/16/2010	Oral tablet Dose: one tablet daily by mouth at the same time every day	-prevent pregnancy -raise folate levels in women who choose to use an oral contraceptive for contraception
Drospirenone 3 mg and ethinyl estradiol 0.03 mg				
Yasmin®	NDA 21-098	5/11/2001	Oral tablet Dose: one tablet daily by mouth at the same time every day	-indicated for use by women to prevent pregnancy
Ocella®	ANDA 77-527	5/9/2008	see Yasmin information	
Zarah®	ANDA 09-0081	9/7/2010		
Syeda®	ANDA 90-114	3/28/2011		
Drospirenone 3 mg and ethinyl estradiol 0.02 mg				
Yaz®	NDA 21-676	3/16/2006	Oral tablet Dose: one tablet daily by mouth at the same time every day	-prevent pregnancy -treat symptoms of premenstrual dysphoric disorder (PMDD) for women who choose to use an oral contraceptive for contraception -treat moderate acne for women at least 14 years old only if the patient desires an oral contraceptive for birth control
Gianvi®	ANDA 78-515	3/30/2009	see Yaz information	
Loryna®	ANDA 79-221	3/28/2011		
Vestura®	ANDA 78-833	11/28/2011		

2 METHODS AND MATERIALS

2.1 DETERMINING SETTING OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for Beyaz. Sales data for year 2011 indicated that

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approximately 91% of packages (Eaches) were distributed to outpatient retail pharmacies; 6% were to mail order pharmacies; and 3% were to non-retail settings.[4] As a result, outpatient retail pharmacy utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

2.2   DATA SOURCES USED

Proprietary drug use databases were used to conduct this analysis (see Appendix 2 for full data descriptions).

IMS, Vector One®: National (VONA) was used to obtain estimates of the number of outpatient dispensed prescriptions for Beyaz and other drospirenone-containing contraceptive products, stratified by age (0-13, 14-17, 18+ years), from September 2010 to March 2012. IMS, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the number of patients receiving a dispensed prescription for Beyaz and other drospirenone-containing contraceptive products, stratified by age (0-13, 14-17, 18+ years), in the outpatient setting from September 2010 to March 2012. Diagnoses associated with the use of Beyaz and other drospirenone-containing contraceptive products, stratified by age (0-13, 14-17, 18+ years), were obtained from the Encuity Research, LLC., Physician Drug and Diagnosis Audit™ (PDDA) from September 2010 to March 2012.   Hormone replacement therapy products (i.e. Angeliq®) were not examined.

3   RESULTS

3.1   OUTPATIENT DISPENSED PRESCRIPTIONS FOR DROSPIRENONE-CONTAINING CONTRACEPTIVE PRODUCTS AND BEYAZ BY PATIENT AGE

Table 1 in Appendix 1 shows the nationally estimated number of dispensed prescriptions for drospirenone-containing contraceptive products by patient age and product (0-13, 14-17, 18+ years) from U.S. outpatient retail pharmacies, September 2010 through March 2012. During the examined time, approximately 19 million prescriptions were dispensed for a drospirenone-containing contraceptive products. Of these prescriptions, approximately 0.3% (52,800 prescriptions) and 8% (1.5 million prescriptions) of total prescriptions were dispensed to the pediatric population aged 0-13 years and 14-17 years, respectively. Gianvi was the most commonly dispensed product, accounting for 34% (6.5 million prescriptions) of total prescriptions followed by Zarah at 16% (3 million prescriptions) and Ocella at 15% (2.9 million prescriptions) of the market, respectively. Beyaz ranked fifth among the drospirenone-containing contraceptive products, accounting for approximately 8% (1.6 million prescriptions) of the total market during the examined time. Similar prescription utilization trends by product were seen in pediatric patients aged 0-17 years during the examined time (Figure 1 in Appendix 1).

From September 2010 through March 2012, approximately 1.4 million prescriptions of Beyaz were dispensed to adults aged 18 years or older. Of the Beyaz prescriptions

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[4] IMS Health, IMS National Sales Perspectives™. Year 2011. Extracted June 2012. File: NSPC 2012-834 beyaz channels.xls

dispensed to pediatric patients, approximately 163,000 prescriptions were dispensed to patients aged 14-17 year and 6,000 prescriptions were dispensed to patients aged 0-13 years.

3.2 PATIENT UTILIZATION OF DROSPIRENONE-CONTAINING CONTRACEPTIVE PRODUCTS AND BEYAZ BY PATIENT AGE

Table 2 in Appendix 1 shows the nationally estimated number of patients who received prescriptions dispensed for drospirenone-containing contraceptive products and Beyaz by patient age from U.S. outpatient retail pharmacies, September 2010 through March 2012. During the examined time, approximately 2.7 million patients received a dispensed prescription for drospirenone-containing contraceptive products. Of these patients, approximately 12% (326,000 patients) received a dispensed prescription for Beyaz. The pediatric population accounted for approximately 12% (39,000 patients) of Beyaz patients. Of the pediatric patients with a dispensed prescription for Beyaz approximately 38,000 patients were aged 14-17 year and 1,889 patients were aged 0-13 years. Adults 18 years or older accounted for approximately 90% (293,000 patients) of Beyaz patients.

3.3 DROSPIRENONE-CONTAINING CONTRACEPTIVE PRODUCTS AND BEYAZ UTILIZATION BY PRESCRIBING SPECIALTY

Obstetrics/Gynecology (Ob/Gyn) was the top prescribing specialty for drospirenone-containing contraceptive products and Beyaz accounting for approximately 52% (9.9 million prescriptions) and 69% (1.1 million prescriptions) of prescriptions dispensed, respectively. Pediatricians accounted for approximately 3% (529,000 prescriptions) of all drospirenone-containing product prescriptions and <1% (8,200 prescriptions) of all Beyaz prescriptions over the entire review period (*Table 3 in Appendix 1*).

3.4 DIAGNOSIS ASSOCIATED WITH THE USE OF DROSPIRENONE-CONTAINING CONTRACEPTIVE PRODUCTS AND BEYAZ BY PATIENT AGE

Diagnoses associated with the use of drospirenone-containing contraceptive products stratified by patient age were coded according to the International Classification of Diseases (ICD-9-CM) and 95% confidence intervals were calculated for the estimates (*Tables 4 in Appendix 1*). According to physician survey data, drug use mentions[5] for "Contracep Mgmt-Counsel" (V250.0) followed by "Dysmenorrhea" (ICD-9 625.3) were the most common diagnosis codes for pediatric patients aged 14-17 years at 26% and 24% of drug use mentions, respectively. Among pediatric patients aged 0-13 years, "Premenopause Menorrhagia" (ICD-9 627.0) was the most common diagnosis code associated with the use of drospirenone-containing contraceptive products during the

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[5] Encuity Research, LLC. uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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review period; however the number of mentions was below the acceptable count allowable to provide a reliable estimate of national use and should therefore be interpreted with caution. For patients aged 18 years and older, approximately 44% of drug use mentions for drospirenone-containing contraceptive products were associated with the health care encounter code of "Contracept Surveillance" (V254.0) and 22% of drug use mentions were associated with health care encounter code "Contracep Mgmt-Counsel" (V250.0) during the study period.

Table 5 in Appendix 1 provides the diagnosis codes associated with the use of Beyaz stratified by patient age from September 2010 through March 2012. Overall, the most common diagnosis codes associated with the use of Beyaz were similar to diagnoses mentioned for drospirenone-containing contraceptive products by patient age. However, "Dysmenorrhea" (ICD-9 625.3) followed by "Contracep Mgmt-Counsel" (V250.0) were the most common diagnosis codes for pediatric patients aged 14-17 years at 43% and 22% of drug use mentions, respectively. Among pediatric patients aged 0-13 years, "Premenopause Menorrhagia" (ICD-9 627.0) was the only diagnosis code captured associated with the use of Beyaz during the review period; however the number of mentions was below the acceptable count allowable to provide a reliable estimate of national use and should therefore be interpreted with caution.

4   LIMITATIONS

Pediatric utilization of Beyaz accounted for 11% (169,000 prescriptions) of Beyaz prescriptions and 12% (39,000 patients) of patients who received Beyaz prescriptions during the examined time. Less than 1% of prescriptions for Beyaz were prescribed by pediatricians while 3% of prescriptions for drospirenone-containing contraceptive products as a whole were prescribed by pediatricians. Although "Contracep Mgmt-Counsel" (V250.0) was the top diagnosis associated with the use of all drospirenone-containing contraceptive products, "Dysmenorrhea" (ICD-9 625.3) was the top diagnosis in Beyaz patients aged 13-17 years, followed by "Contracep Mgmt-Counsel" (V250.0) during the review period.

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that Beyaz was distributed primarily in outpatient settings based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use. We focused our analysis on only the outpatient retail pharmacy setting, therefore these estimates may not apply to other settings of care in which these products are used (e.g. mail order).

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) data provide estimates of patient demographics and indications for use of medicinal products in the U.S. Due to the sampling and data collection methodologies, the small sample size can make these data unstable, particularly if use is not common in the pediatric population.

Although PDDA data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, PDDA data are best used to identify the typical uses for the products in clinical practice. Encuity Research, LLC. recommends caution interpreting projected annual uses or mentions below 100,000 as the sample size is very small with correspondingly large confidence intervals.

5   CONCLUSIONS

Pediatric utilization of Beyaz accounted for 11% (169,000 prescriptions) of Beyaz prescriptions and 12% (39,000 patients) of patients who received Beyaz prescriptions during the examined time. Beyaz was the fifth most commonly dispensed drospirenone-containing contraceptive product in patients aged 0-17 years.

6   APPENDICES

6.1   APPENDIX 1: TABLES AND FIGURES

Table 1. Nationally estimated number of dispensed prescriptions for Drospirenone contraceptive market by patient age (0-13, 14-17, 18+) in U.S. outpatient retail pharmacies, September 2010-March 2012

	09/2010-03/2012	
	TRxs	**Share**
	N	**%**
Drospirenone	**18,970,934**	**100.0%**
Age 0-13 yrs	52,841	0.3%
Age 14-17 yrs	1,502,976	7.9%
18+ yrs	17,414,694	91.8%
Unknown Age	423	0.0%
Gianvi	**6,503,735**	**34.3%**
Age 0-13 yrs	23,229	0.4%
Age 14-17 yrs	644,190	9.9%
18+ yrs	5,836,273	89.7%
Unknown Age	43	0.0%
Zarah	**3,090,060**	**16.3%**
Age 0-13 yrs	7,041	0.2%
Age 14-17 yrs	173,417	5.6%
18+ yrs	2,909,600	94.2%
Unknown Age	2	0.0%
Ocella	**2,875,264**	**15.2%**
Age 0-13 yrs	6,470	0.2%
Age 14-17 yrs	181,188	6.3%
18+ yrs	2,687,461	93.5%
Unknown Age	146	0.0%
Yaz	**2,685,240**	**14.2%**
Age 0-13 yrs	4,907	0.2%
Age 14-17 yrs	198,094	7.4%
18+ yrs	2,482,053	92.4%
Unknown Age	187	0.0%
Beyaz	**1,565,235**	**8.3%**
Age 0-13 yrs	6,073	0.4%
Age 14-17 yrs	163,052	10.4%
18+ yrs	1,396,070	89.2%
Unknown Age	39	0.0%
Yasmin 28	**1,005,955**	**5.3%**
Age 0-13 yrs	1,776	0.2%
Age 14-17 yrs	38,059	3.8%
18+ yrs	966,114	96.0%
Unknown Age	5	0.0%
Loryna	**685,120**	**3.6%**
Age 0-13 yrs	1,752	0.3%
Age 14-17 yrs	64,330	9.4%
18+ yrs	619,038	90.4%
Syeda	**361,114**	**1.9%**
Age 0-13 yrs	778	0.2%
Age 14-17 yrs	23,932	6.6%
18+ yrs	336,403	93.2%
Unknown Age	1	0.0%
Safyral	**198,203**	**1.0%**
Age 0-13 yrs	809	0.4%
Age 14-17 yrs	16,567	8.4%
18+ yrs	180,826	91.2%
Vestura	**1,008**	**0.0%**
Age 0-13 yrs	6	0.6%
Age 14-17 yrs	146	14.5%
18+ yrs	855	84.9%

Source: IMS Vector One®: National, Sep 2010-Mar 2012 Data Extracted June 2012.   File: VONA 2012-834 DRSP by prod age 6-5-12; VONA 2012-834 DRSP by age 6-6-12

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Figure 1. Nationally estimated number of prescriptions for drospirenone contraceptive market dispensed to patients aged 0-17years, by product, from U.S. outpatient retail pharmacies, September 2010-March 2012

Source: IMS Vector One®: National, Sep 2010-Mar 2012 Data Extracted June 2012.

(Dispensed prescriptions by product:)

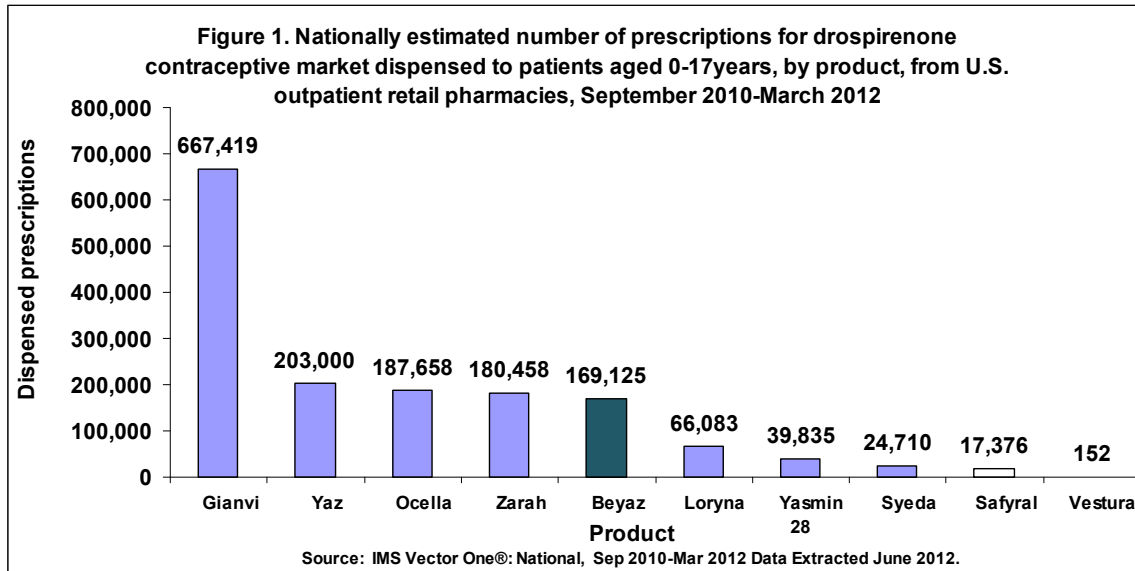| Product	Dispensed prescriptions
Gianvi	667,419
Yaz	203,000
Ocella	187,658
Zarah	180,458
Beyaz	169,125
Loryna	66,083
Yasmin 28	39,835
Syeda	24,710
Safyral	17,376
Vestura	152

Table 2. Nationally estimated number of patients who filled a prescription for the drospirenone contraceptive market and Beyaz, by patient age, in U.S. outpatient retail pharmacies, September 2010-March 2012

	09/2010-03/2012	
	Patient Count	*Share*
	N	*%*
Drospirenone	**2,675,119**	*100.0%*
Age 0 - 17 yrs	**275,913**	*10.3%*
Age 0 - 13 yrs	13,991	*5.1%*
Age 14 - 17 yrs	266,675	*96.7%*
Age 18+ yrs	2,465,185	*92.2%*
Unknown Age	179	*0.0%*
Beyaz	**325,945**	*12.2%*
Age 0 - 17 yrs	**38,942**	*11.9%*
Age 0 - 13 yrs	1,889	*4.9%*
Age 14 - 17 yrs	37,571	*96.5%*
Age 18+ yrs	292,749	*89.8%*
Unknown Age	33	*0.0%*
All Other Products	**2,349,174**	*87.8%*

Source: IMS Total Patient Tracker. Sep 2010-Mar 2012 Data Extracted June 2012.
File: TPT 2012-834 Beyaz by age 6-5-12; TPT 2012-834 DRSP by age 6-5-12,
TPT 2012-834 all dros total 0-17.xls, and TPT 2012-834 Beyaz total 0-17.xls

Note: IMS does not recommend adding across unique patient counts. Summing across patient age bands is not advisable and can result in overestimates of calculations.

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Table 3. Nationally estimated number of dispensed prescriptions for the drospirenone contraceptive market and Beyaz in outpatient retail pharmacies by top 10 prescribing specialties, September 2010-March 2012

| | 09/2010-03/2012 | |
| | TRxs | Share |
	N	%
Drospirenone Contraceptive Market	**18,970,934**	**100.0%**
OB/GYN	9,885,709	52.1%
NP	2,632,135	13.9%
GP/FM/DO	2,571,704	13.6%
UNSPEC	853,633	4.5%
PA	775,663	4.1%
IM	770,572	4.1%
PED	528,876	2.8%
DERM	341,490	1.8%
OTHER	120,084	0.6%
ENDO	102,382	0.5%
All Others	388,685	2.0%
Beyaz	**1,565,235**	**100.0%**
OB/GYN	1,085,246	69.3%
NP	229,829	14.7%
UNSPEC	68,416	4.4%
GP/FM/DO	67,242	4.3%
PA	44,227	2.8%
IM	14,046	0.9%
DERM	13,698	0.9%
PED	8,239	0.5%
OTHER	7,064	0.5%
HOSP	5,595	0.4%
All Others	21,633	1.4%

Source: IMS Vector One®: National, Sep 2010-Mar 2012 Data Extracted June 2012. File: VONA 2012-834 Beyaz by MD 6-5-12 and VONA_2012-834_all_dros_contraceptive total_by_MD,_june2012.xls *GP/FM/DO – General Practice, Family Medicine, Doctor of Osteopathy

Table 4. Diagnoses associated with the use* of Drospirenone by patient age (0-13, 14-17, 18+) as reported by office-based physician practices, September 2010-March 2012

	09/2010-03/2012		
		95% Confidence Interval	
	Uses (000)	Uses (000)	Share%
Drospirenone	**7,499**	**7090-7,908**	**100.0%**
Age 0-13 yrs	**44**	**13-76**	**0.6%**
6270 PREMENOPAUSE MENORRHAGIA	14	<0.5-31	30.4%
6260 ABSENCE OF MENSTRUATION	10	<0.5-26	23.2%
2564 POLYCYSTIC OVARIES	10	<0.5-26	23.2%
V254 CONTRACEPT SURVEILLANCE	10	<0.5-25	23.1%
Age 14-17 yrs	**388**	**295-481**	**5.2%**
V250 CONTRACEP MGMT-COUNSEL	101	53-148	25.9%
6253 DYSMENORRHEA	92	47-138	23.8%
V254 CONTRACEPT SURVEILLANCE	72	32-112	18.6%
7061 ACNE NEC	33	6-61	8.6%
6264 IRREGULAR MENSTRUATION	26	2-51	6.8%
V723 GYNECOLOGIC EXAMINATION	21	<0.5-43	5.5%
6266 METRORRHAGIA	14	<0.5-32	3.7%
2564 POLYCYSTIC OVARIES	12	<0.5-28	3.1%
6262 EXCESSIVE MENSTRUATION	7	<0.5-20	1.9%
6263 PUBERTAL MENORRHAGIA	6	<0.5-17	1.5%
All Others	2	<0.5-10	0.6%
Age 18+ yrs	**6,904**	**6,512-7,297**	**92.1%**
V254 CONTRACEPT SURVEILLANCE	3,011	2,752-3,270	43.6%
V250 CONTRACEP MGMT-COUNSEL	1,542	1,356-1,728	22.3%
V723 GYNECOLOGIC EXAMINATION	1,312	1,141-1,484	19.0%
V242 ROUT POSTPART FOLLOW-UP	151	93-209	2.2%
V258 CONTRACEPTIVE MANGMT NEC	122	70-175	1.8%
2564 POLYCYSTIC OVARIES	112	62-162	1.6%
6264 IRREGULAR MENSTRUATION	99	52-147	1.4%
6253 DYSMENORRHEA	98	51-144	1.4%
6254 PREMENSTRUAL TENSION	90	45-134	1.3%
All Others	367	277-458	5.3%
UNSPEC	162	102-223	2.2%

Source: Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel, Sep 2010-Mar 2012 Extracted June 2012. File: PDDA 2012-834 DRSP by AgeDx4 6-5-12

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

Note: SDI recommends caution interpreting national estimates of drug uses below 100,000 as the sample size is very small with corresponding large confidence intervals

Table 5. Diagnoses associated with the use* of Beyaz by patient age (0-13, 14-17, 18+) as reported by office-based physician practices, September 2010-March 2012

	09/2010-03/2012		
	Uses (000)	95% Confidence Interval Uses (000)	Share%
Beyaz	**1,685**	**1,491-1,879**	**100.0%**
Age 0-13 yrs	**14**	**<0.5-31**	**0.8%**
6270 PREMENOPAUSE MENORRHAGIA	14	<0.5-31	100.0%
Age 14-17 yrs	**160**	**101-220**	**9.5%**
6253 DYSMENORRHEA	69	29-108	42.8%
V250 CONTRACEP MGMT-COUNSEL	35	7-63	21.6%
6264 IRREGULAR MENSTRUATION	22	<0.5-44	13.5%
V254 CONTRACEPT SURVEILLANCE	19	<0.5-40	12.0%
7061 ACNE NEC	10	<0.5-26	6.5%
V723 GYNECOLOGIC EXAMINATION	6	<0.5-17	3.6%
18+ yrs	**1,472**	**1,290-1,653**	**87.4%**
V250 CONTRACEP MGMT-COUNSEL	586	472-700	39.8%
V254 CONTRACEPT SURVEILLANCE	424	327-521	28.8%
V723 GYNECOLOGIC EXAMINATION	229	157-301	15.6%
V242 ROUT POSTPART FOLLOW-UP	47	15-80	3.2%
6253 DYSMENORRHEA	33	6-60	2.3%
6254 PREMENSTRUAL TENSION	26	2-49	1.7%
2564 POLYCYSTIC OVARIES	22	<0.5-45	1.5%
6264 IRREGULAR MENSTRUATION	18	<0.5-38	1.2%
6262 EXCESSIVE MENSTRUATION	18	<0.5-38	1.2%
All Others	69	29-108	4.7%
UNSPEC	39	10-69	2.3%
V254 CONTRACEPT SURVEILLANCE	39	10-69	100.0%

Source: Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel, Sep 2010-Mar 2012 Extracted June 2012. File: PDDA 2012-834 Beyaz by AgeDx4 6-5-12

* Use - Projected uses for a product linked to a diagnosis. The projected number of times a product has been reported for treatment of a particular disease.

Note: SDI recommends caution interpreting national estimates of drug uses below 100,000 as the sample size is very small with corresponding large confidence intervals

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6.2 APPENDIX 2: DRUG USE DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS, Vector One®: National (VONA)

The IMS, Vector One®: National (VONA) database measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

Prescriptions are captured from a sample from the universe of approximately 59,000 pharmacies throughout the U.S. There are over 800,000 physicians in the VECTOR One database, which supplies VONA, TPT, & DET. The pharmacies in the database account for most retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. IMS receives all prescriptions from approximately one-third of stores and a significant sample of prescriptions from many of the remaining stores.

IMS, Vector One®: Total Patient Tracker (TPT)

The IMS, Vector One®: Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time.

TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 1.9 billion prescription claims per year, representing over 158 million unique patients. Since 2002 Vector One® has captured information on over 15 billion prescriptions representing over 356 million unique patients.

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Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA)

Encuity Research, LLC., Physician Drug & Diagnosis Audit (PDDA) with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

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/s/

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